## REMARKS

CLAIM AMENDMENTS

Claim 20-42 are pending and stand finally rejected. Independent Claims 20 and 29 are amended by the foregoing amendment to clarify that these claims are directed to specific embodiments of Applicant's invention, which are described at p. p. 4, lines 13-21, and in Tables 3, 4 and 5 on p. 14, 15, and 16, respectively. The foregoing amendment also adds (a) new dependent Claims 43-46, which are directed to other specific embodiments of Applicant's invention. The embodiments claimed in Claims 43 and 44 are described at p. 4, line 16 and Tables 3-5, respectively; while the embodiment set forth in Claims 45 and 46 is described at p. 7, lines 19-28. No new matter is contained in the foregoing amendment, and its entry is respectfully requested.

DOUBLE PATENTING REJECTIONS

As noted above, the present application was filed on October 16, 2001 and claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Application Serial No. 60/241,557, filed October 18, 2000.

Claims 20-42 stand provisionally rejected under the judicially-created doctrine of obviousness type double patenting over claims in co-pending, commonly-owned application Serial No. 09/464,426 corresponding to **U.S. pre-grant publication No. US 2002/0119122** which has issued as **U.S. Patent No. 6,824,768**. A Terminal Disclaimer executed by the undersigned attorney of record in compliance with 37 C.F.R. 1.321(c) is submitted herewith, and Applicant respectfully requests removal of this double patenting rejection.

Claims 20-42 stand provisionally rejected under the judicially-created doctrine of obviousness type double patenting over Claims 1-70 in co-pending, commonly-owned application Serial No. 10/255,442 corresponding to **U.S. pre-grant publication No. US 2003/0039630**. If necessary, Applicants will provide a terminal disclaimer to obviate this provisional rejection at the time the rejections under 35 U.S.C. §102 and §103 are removed.

Claims 20 and 29 stand provisionally rejected under the judicially-created doctrine of obviousness type double patenting over Claims 3-7 in co-pending, commonly-owned application Serial No. 09/837,491 corresponding to **U.S. pre-grant publication No. US 2002/0055473.** If necessary, Applicants will provide a terminal disclaimer to obviate the provisional obviousness double patenting rejection at the time the rejections under 35 U.S.C. §102 and §103 are removed.

CLAIM REJECTIONS - 35 USC §102

Claims 20-42 are rejected under 35 U.S.C. §102(a) as being anticipated by **Glue and Albrecht, WO 00/37110 (Glue 1)** or **Glue *et al.*, *Hepatology*, 32(3):647-653, September 2000 (Glue 2)**. Applicant respectfully traverses these rejections for the following reasons.

A claim is anticipated under 35 U.S.C. §102 "only if each and every element of the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131, *quoting* Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Any element of a claim that is not expressly described in the reference must be shown to be *necessarily present* in that reference. *See, e.g., Continental Can Co. USA, Inc. v. Monsanto Co.*, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *MEHL/Biophile Intl. Corp. v. Milgraum*, 192 F.3d 1362, 1365, 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (*citing In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The present invention is based on Applicant's discovery that the efficacy of treating chronic HCV infection with a combination of interferon and ribavirin is related to both the dose per kg of interferon and the dose per kg dose of ribavirin, and further that the efficacy of such combination therapy is significantly increased when the amount of ribavirin administered is greater than 10.6 mg/kg. *See* p. 14, lines 1 to 15 of the specification. Thus, Claims 20-46 comprise administering ribavirin and pegylated interferon alfa-2b protein to a patient with chronic HCV infection in amounts that are based on the patient's body weight. The amounts specified in the present Claims are (a) 1.5 mg/kg of pegylated interferon alfa-2b protein and (b) either (i) one of three specified ribavirin doses depending on which one of three specified weight

ranges that the patient's weight falls within (Claims 20-29, 46) or greater than 10.6 mg ribavirin/kg of the patient's body weight (Claims 29-45).

**Glue 1** generally discloses a method of treating patients for chronic hepatitis C by administering pegylated interferon alpha in association with ribavirin during *two* treatment time periods: a first "induction period" in which the administered amounts of ribavirin and interferon are effective to substantially lower detectable HCV-RNA levels and a second time period in which the administered amounts of ribavirin and interferon are effective to eradicate detectable HCV RNA by a specified time after the end of the first treatment period and to maintain no detectable HCV RNA for a specified time after the end of the second treatment period. See paragraph bridging pp. 3-4. This reference teaches that therapeutically effective amounts of ribavirin include about 400-1200 mg per day for the first treatment period and about 800-1200 mg/day for the second treatment period. *See, e.g.*, p. 6, lines 11-24. **Glue 1** also describes *planned* studies in which ribavirin *would be* administered in a dose of 1000-1200 mg/kg/day. *See* pp. 17-21. The reference does not discuss the weight range of the patients to be included in the planned studies, and Applicant notes that the proposed ribavirn dosage regimen was likely a typographical error, since it would result in an unusually, and probably intolerably, high ribavirin dose.

Thus, there is no express description or even suggestion in **Glue 1** that adjusting the dose for both the pegylated interferon and ribavirin based on the patient's weight would improve the efficacy of the prior known combination therapy. In addition, this reference does not expressly describe either administering ribavirin in one of *three* specific doses based on the patient's body weight falling within one of *three* specific weight ranges, or administering greater than 10.6 mg/kg ribavirin. The claimed regimen would also not *necessarily* result from administering ribavirin in either of the two broad dose *ranges* taught in **Glue 1**. For example, the **Glue 1** regimen could result in treating a patient weighing greater than 85 kg with a dose of 800 mg/day rather than about 1200 mg/day or greater than 10.6 mg/kg/day required by the present claims. Similarly, the **Glue 1** regimen could result in treating a patient weighing about 60 kg to 65 kg with 1200 mg/day ribavirin rather than the 800 mg/day specified in Claim 20.

At best, **Glue 1** suggests trying interferon/ribavirin combination therapy using 1000-1200 mg/kg/day of ribavirin. However, this one dosage range would not *inherently* produce the instantly claimed ribavirin dose/kg for *every* patient. For example, administering ribavirin at 1000 mg/kg to a patient having a weight of about 60 kg to 65 kg would result in the patient receiving more than the 800 mg/day specified in Claim 20.

Similarly, the presently claimed treatment regimen is not expressly or inherently disclosed by **Glue 2**. This reference describes a study that "assessed the "safety, tolerability, pharmacokinetics, and pharmacodynamics of combined PEG-Intron and ribavirin in patients with chronic hepatitis C" (p. 647, 2nd paragraph of the 2nd column). The amount of PEG-Intron administered was 0.35, 0.7, or 1.4 μg/kg, which is less than the presently claimed 1.5 μg/kg of pegylated interferon alfa 2b (p. 648, 1st paragraph of the 1st column). The ribavirin dose administered was either 600 mg/d, 800 mg/d or 1,000-1,200 mg/d, without any adjustment for the weight of the patient as required by the present claims. Moreover, Glue 2 states that "[a]t the highest ribavirin dose level, patients weighing less than 75 kg received 1,000 mg/d and those weighing 75 kg or more received 1,200 mg/d" (p. 648, 1st paragraph of the 1st column). Thus, none of the treatment regimens studied by Glue 2 inherently produces the Claim 20 treatment regimen of only 800 mg/day for a patient weighing about 60 kg to 65 kg. In addition, while Glue 2 states that "the anti-HCV activity of PEG-Intron appeared to be enhanced by the addition of ribavirin" (p. 650, 3rd paragraph of 2nd column), Glue 2 explicitly state that "[b]ecause of the small numbers of patients in each ribavirin dose level, it was not possible to assess the effect of ribavirin dose on antiviral responses" (p. 652, 1st full paragraph of 2nd column). Thus, since the efficacy data was generated by pooling all the ribavirin doses (see Fig. 3 and Table 3), the skilled artisan could not discern from Glue 2 whether any of the treatment regimens inherently produced the eradication of detectable HCV-RNA by the end of the treatment period and the subsequent maintenance of no detectable HCV RNA as required by the present claims.

For the foregoing reasons, neither **Glue 1** nor **Glue 2** anticipates the present invention, and Applicant respectfully requests reconsideration and withdrawal of these rejections under 35 U.S.C. §102.

In addition, neither Glue 1 nor Glue 2 expressly or inherently discloses the per kg doses specified in new Claims 43 and 44, and thus Claims 43 and 44 are patentable over each of these references.

CLAIM REJECTIONS - 35 USC §103

Claims 20-42 are rejected under 35 U.S.C. §103(a) as being unpatentable over any of the following primary references: **Davis *et al.*, *N Engl J Med*, 339:1493-1499, 1998, McHutchison *et al.*, *N Engl J Med*, 339:1485-1492, 1998, Poynard *et al.*, *Lancet*, 352:1426-1432, 1998,** or **Reichard *et al.*, *Lancet*, 351:83-87,** 1998, when combined with **Gilbert, WO 95/13090.** Applicant respectfully traverses these rejections because the Office Action has not established a *prima facie* case of obviousness.

As stated in the MPEP, §706.02(j), three criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation to modify a single reference or to combine the teachings of more than one reference. Second, there must be a reasonable expectation of success. Third, the modified prior art reference or combination of references must teach or suggest *all* the claim limitations. Each of the first and second criteria can not be based on applicant's disclosure, but must be found in the prior art, or based on the knowledge generally available to one of ordinary skill in the art.

As discussed above, Claims 20-46 comprise administering ribavirin and pegylated interferon alfa-2b protein to a patient with chronic HCV infection in amounts that are based on the patient's body weight. The amounts specified in the present Claims are (a) 1.5 mg/kg of pegylated interferon alfa-2b protein and (b) either (i) one of three specified ribavirin doses depending on which one of three specified weight ranges that the patient's weight falls within (Claims 20-29, 46) or greater than 10.6 mg ribavirin/kg of the patient's body weight (Claims 29-45)

Each of the primary references describes treating chronic HCV by administering: (a) 3 million units of interferon alfa-2b three times a week and (b) 1000 mg/day of ribavirin for patients who weigh 75 kg or less or 1200 mg/day of ribavirin for patients who weigh more than

75 kg. Gilbert describes that pegylated forms of interferon alpha retain all of the biological activity as the unconjugated forms and are longer acting. The combination of either of these primary references with Gilbert merely suggest replacing the *non-pegylated* interferon alfa used in the Davis et al. treatment regimen with *pegylated* interferon alfa 2b; however, these references, alone or combination, do not teach or suggest the *particular* combination of (a) a weight-based pegylated interferon dose and (b) specific weight based ribavirin doses used in the presently claimed methods.

With respect to the ribavirin component of this combination, the Office Action alleges that the skilled artisan would be motivated to modify the Davis et al. reference to identify other ribavirin doses just because the reference allegedly identifies patient weight as a determining factor. However, since each of the primary references teach that its treatment regimen was efficacious, Applicant respectfully asserts that the Office Action's reasoning amounts to no more than an "obvious to try" argument, which is insufficient to establish a *prima facie* case of obviousness, and also impermissibly relies on Applicant's disclosure to conclude that somehow the skilled artisan would have identified, from the almost infinite number of combinations that could be envisioned, the *particular* combination of weight-based pegylated interferon and ribavirin doses that are specified in the present claims. Indeed, the primary references do not teache or suggest that *increasing* the amount of ribavirin increases the efficacy of combined interferon/ribavirin therapy; thus these references provides no motivation to derive a dose of 1200 mg/d for a patient weighing greater than 85 kg (Claim 20), or to administer ribavirin in an amount of greater than 10.6 mg/kg (Claim 29). In addition, even if the skilled artisan had somehow selected the *particular* combination of pegylated interferon alpha-2b and ribavirin dose that is specified in the present claims, the Office Action fails to explain why the skilled artisan would have had any expectation that such combination would be effective, particularly a ribavirin dose of only 800 mg for a patient weighing between about 60 kg to 65 kg, which is less than the lowest dose taught by the primary references.

With respect to the pegylated interferon component of the presently claimed combination therapy, the Office Action alleges that the 3M units of *non-pegylated* interferon alfa used in the treatment regimen disclosed in the primary references is equivalent to the 1.5 μg/kg of *pegylated* interferon alfa 2b used in the presently claimed method because these prior art treatment

regimens allegedly produced "a sustained virologic response." Applicant respectfully asserts that such a comparison, even if correct, would be relevant for an anticipation by inherency rejection, but is not appropriate for a rejection based on obviousness. Since no direct translation is available to convert 3 million units of interferon alfa to its equivalent in micrograms/kg, the Office Action fails to set forth a reason why the skilled artisan would have had a reasonable expectation that the particular claimed weight-based dose of *pegylated* interferon would produce the claimed antiviral response when combined with the particular weight-based ribavirin doses specified in the present claims.

In conclusion, Applicants assert that none of the primary references taken alone or in combination with Gilbert teach or suggest all the limitation of the present claims, nor provide any expectation that the presently claimed weight-based combination therapy would produce the claimed antiviral response.

**Information Disclosure Statement**

Applicants submit herewith an information disclosure statement, which cites an abstract authored by Glue et al, published sometime in October 1999. Even if this reference constitutes prior art, Applicant respectfully asserts that it does not teach or suggest the presently claimed invention. For example, the treatment regimen disclosed in this abstract uses only 1.4 μg/kg pegylated interferon rather than the 1.5 μg/kg required by the present claims. Thus, this abstract does not teach or suggest the particular combination of weight-based pegylated interferon and ribavirin specified in the present claims. This abstract also does not teach or suggest that any of the disclosed treatment regimens would achieve the claimed antiviral response of maintaining no detectable HCV RNA for at least 12 weeks post treatment.

## CONCLUSION

Applicant respectfully asserts that the foregoing is fully responsive to the outstanding office action, and respectfully request consideration of the amended claims in view of the newly cited Glue et al. abstract.

Respectfully submitted,

Melodie W. Henderson

SCHERING-PLOUGH CORPORATION
Patent Department, K-6-1, 1990
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530

Melodie W. Henderson
Reg. No. 37,848
Attorney for Applicant
(908) 298-7482

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